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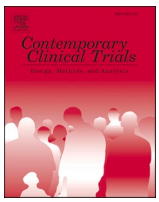

DiabeText, a mobile health intervention to support medication taking and healthy lifestyle in adults with type 2 diabetes: Study protocol for a randomized controlled trial

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Aim: To evaluate the effectiveness of DiabeText, a low-intensity, multifaceted, mobile health (mHealth) intervention to support medication taking and lifestyle change targeted to people with type 2 diabetes (T2D).
Design: Phase III, 12-months, two-arm (1:1 allocation ratio), randomized parallel-group trial.
Methods: We will recruit 740 adults with glycated hemoglobin (A1c) >8% (>64 mmol/mol) and with at least one prescription of a non-insulin antidiabetic drug. They will be allocated to a control (usual care) group or an intervention (DiabeText messaging intervention) group. The primary outcome measure will be A1c at 12 months follow-up. Secondary outcomes will include medication possession ratio and behavioral and psychological outcomes.
Discussion: Recent trials suggest that digital health interventions can effectively support diabetes self-management improving T2D control and reducing important T2D complications. In Spain this type of interventions is understudied.
Impact: This trial will strengthen the evidence base of the impact of mHealth interventions to support diabetes self-management. If effective, DiabeText may offer a low-cost and highly scalable strategy to improve health at the population level in a sustainable way.
Trial registration: ClinicalTrials.gov identifier NCT05006872; Official Title: Supporting People with Type 2 Diabetes in Effective Use of their Medicine Through a System Comprising Mobile Health Technology Integrated with Clinical Care.

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1. Introduction

Type 2 diabetes (T2D) is a serious, chronic condition that accounts for the vast majority (over 90%) of diabetes worldwide and ranks among the top causes of premature death. People with T2D are at high risk of developing serious complications (e.g., blindness, lower-limb amputations, kidney disease, and cardiovascular disease), which reduce their quality of life and life expectancy. Europe accounts for 61 million people with diabetes, 5.1 million people living in Spain [1,2]. T2D and its complications are the cause of major expenditure for the Spanish National Health Service (SNHS): yearly, 8.2–12.8% of total expenditure is spent on direct costs [3], in addition to other indirect costs of diabetes-related complications [4] and labour productivity losses [5].

2. Background

T2D can be prevented or delayed, and there is accumulating evidence that remission may sometimes be possible [1]. The cornerstone of T2D management is lifestyle modification including a healthy diet, regular physical activity, smoking cessation and maintenance of healthy body weight and, medication treatment. However, the implementation in the health care setting of interventions to support diabetes self-management (DSM) in people with T2D still remains an important challenge added to that the knowledge of patients about diabetes and its treatment remains insufficient among the Spanish population [6].

One potential solution to this complex problem could be mobile health (mHealth) interventions. Health interventions delivered via mobile devices offer a new approach and have the potential to support medication taking [7], glycemic control [8] and diabetes self-management [9]. Automated messages delivered via such devices can potentially target a wide range of beliefs and behaviors over a long period of time, making the interventions wide-ranging and low-cost. The content of mHealth interventions can also be personalized based on data from electronic health records (EHRs) and patient-reported data, and therefore, this type of intervention has great potential for delivering personalized health services, which is a current priority for most healthcare systems worldwide.

Currently, there is a lack of strong evidence about the clinical effectiveness [10,11], safety and cost-efficiency [12] of mHealth interventions to support type 2 diabetes self-management. Also, although recent research offers indications that receiving text messages is associated with changes in psychological variables that are predictive of medication adherence [13], it is still unclear which are the most active ingredients driving behavior change [14].

In Spain, 99.2% of adult citizens are mobile phone users [15]. Therefore, interventions based on the use of SMSs have the potential to reach a very large proportion of the Spanish population. To our knowledge, DiabeText is the first study evaluating the impact on glycemic control, medication taking and lifestyle of a tailored mHealth intervention to support type 2 diabetes care in Spain.

3. The study

3.1. Aim

To assess the effectiveness of DiabeText, a low-intensity, multifaceted, digital health intervention to support medication taking and lifestyle changes addressed to people with T2D and blood glycemic A1c > 8%, based on the use of a system comprising mHealth technology integrated with EHRs to send tailored SMSs, on glycemic control, lifestyle change and medication taking.

3.2. Objectives

1. To test the effectiveness of DiabeText through a phase III, 12-month, randomized controlled trial (RCT) on glycemic control measured as a percentage of A1c reduction.
2. To explore the effects of DiabeText on medication taking measured as medication possession ratio (MPR) for antidiabetic drugs, patient-reported adherence to diabetes medication, quality of life, self-efficacy to manage diabetes, adherence to the Mediterranean diet, and physical activity level.
3. To carry out a qualitative interview study with participants to explore the acceptability of DiabeText and to inform its optimization and large-scale implementation.

3.3. Hypothesis

An intervention based on the use of a mobile-device-based system delivering automated, tailored brief messages to offer support for medicine use to people with T2D reduces A1c levels by at least 4 mmol/mol (0.4%) in the intervention group compared with the control group (receiving usual care) after 12 months follow-up. Moreover, compared with the control group, the proposed intervention improves MPR and patient-reported adherence to diabetes medication, quality of life, self-efficacy to manage diabetes, adherence to Mediterranean diet and physical activity level. Finally, the proposed intervention is acceptable to patients and could be implemented in the Primary Care setting.

3.4. Trial design

The DiabeText study is a phase III, 12-month, two-arm (1:1 allocation ratio), randomized parallel-group trial. In the intervention group, patients will receive the text messaging intervention. Control group participants will receive usual care only.

3.5. Participants and recruitment strategy

Participants' identification will be carried out with support from the Health Information Research Platform from the Balearic Islands (PRISIB), from which the list of possible candidates for the study will be extracted. Potential participants will receive an SMS on their mobile phones, containing a link to a website, inviting them to participate in the study. The website will include a brief summary of the study, the patient information sheet and the informed consent (see Supplementary material 1). Two days later, a research assistant will contact the potential participants via phone to check if they received the invitation correctly. For those potential participants who could not accede to the website, the information will be read or sent by alternative ways (e-mail or WhatsApp). During the phone call, if the person wants to participate in the study, the recruiter will check eligibility criteria and record the informed consent. After that, the basal interview could be completed.

3.6. Eligibility criteria

Selection criteria: we will include primary care patients aged >18 years, with T2D, blood glycemic A1c >8% (>64 mmol/mol) recorded during the previous 6 months, with at least one prescription of a non-insulin antidiabetic drug and able to receive, read and understand SMS in Spanish through a mobile phone. We will not exclude patients based on the time of diagnosis of diabetes – i.e., we will include patients with an active register of diabetes at any time. We will exclude those with severe mental conditions, participating in another research study, or not living in the Balearic Islands at some point during the study development.

3.7. Intervention

Participants allocated to the intervention group will receive SMS text messages specifically designed for this study based on: 1) systematic reviews about the efficacy and development process of mHealth intervention targeted at patients with T2D [16–18]; 2) a qualitative study involving both healthcare providers and people with T2D [19,20] and 3) a retrospective study of predictors of non-adherence to antidiabetic medication [21]. Messages were developed in a multistage and iterative process involving four workshops with a multidisciplinary team, an expert panel and people with T2D who reviewed each SMS to ensure its appropriateness and understanding [22]. Contents were based on the Standards of Medical Care in Diabetes [23–26]. Supplementary materials 2 and 3 include respectively the template for DiabeText intervention description and replication checklist [27] and examples of SMS text messages along with the corresponding behavioral change technique that the message is intended to target according to the Behavior Change Wheel framework [28,29].

Participants in the intervention group will be sent up to 5 automated SMS text messages per week, with an average frequency of 3 per week, related to diabetes management and the use of medicine for twelve months. The amount of messages with medication information will be 50% of total intervention while the amount of messages about dietary advice and physical activity will be tailored according to baseline lifestyle assessment. Messages will also be tailored according to participants' clinical data such as the presence of other chronic diseases or diabetes-related complications. Participants will also receive messages with the latest blood test results, changes in body weight and reminders for medical appointments and pharmacy medication pickup. Correct reception of messages by participants will be tracked to ensure an optimum intervention reaches all intervention group participants. The control group will receive usual care only. All participants will continue with their usual diabetes care including medical visits, tests, and diabetes support programs throughout the study.

3.8. Outcome measures

The primary outcome is A1c (%) at 12-month follow-up. Secondary outcome measures will include: MPR (% of medication available), the proportion of participants with good adherence to medication (MPR > 80%); self-reported adherence to diabetes medication (measured with an ad hoc questionnaire adapted from Chaves-Torres et al. for people with T2D [30]); health-related quality of life (5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L) index score [31]; self-efficacy, (diabetes management self-efficacy scale in Spanish (DSES-S)) [32]; adherence to the Mediterranean diet (14-point Mediterranean Diet Adherence Screener (MEDAS-14) questionnaire) [33]; and physical activity (6-item International Physical Activity Questionnaire (IPAQ)) [34]. These outcomes will reflect how participants adhere to their treatment plans from both a biological and a behavioral point of view.

3.9. Participant timeline

Recruitment will be carried out by a group of 15–20 trained research assistants supervised by the trial manager (RZC). Potentially eligible participants will receive the invitation by SMS. After 2–7 days the research assistants will contact the potential participants via phone. On this call, patients will be offered complete information on the study and, if willing to participate, they will record the informed consent. On the same call, baseline interviews and randomization will be performed. Patients will then be informed of their allocation. Interviews will last 40 min approximately.

Based on the results from our previous phase II trial [21], we anticipate a maximum delay of two months between enrollment and message start. Once the recruitment is completed, all participants will simultaneously initiate the follow-up period. After the twelve-month follow-up, data from patients will be collected following the same procedure as at baseline interview. Fig. 1 shows the schedule of enrolment, interventions, and assessments of the trial.

3.10. Sample size

We estimate that a sample of 740 participants (370 per group) would allow us to detect changes in A1c between groups of 4 mmol/mol (0.4%) based on a standard deviation of 15 mmol/mol (1.5%). This estimate includes a 20% loss to follow up at 90% power and $p = 0.05$. This number of participants will also provide us with 80% power to detect an increase in the proportion of medication available from a baseline of 50% to 60.9%.

3.11. Randomization and masking

After recruitment, individual randomization will be conducted using the Spanish adaptation of the free OxMaR software for randomization of clinical studies [35,36]. Allocation will be carried out using a non-deterministic minimization algorithm to ensure intervention groups are balanced for important baseline prognostic factors such as age and sex. Both care providers and research staff will be blinded to treatment allocation during the intervention trial, and for the collection of outcomes and data analysis. Participants won't be blinded because of the nature of the intervention.

3.12. Data collection and management

The data from patients at baseline and after the 12 months follow-up will be collected by telephone interviews, and registered in an online registry platform.

Data about the intervention's reach to participants will be collected through the message-sending platform *Bitmessage* periodically and, at the end of the study.

3.13. Data analysis

We will use descriptive statistics to examine the sociodemographic and clinical characteristics of the participants (overall and by randomized group). Mean, standard deviation, and frequencies will be used to present categorical and continuous variables respectively. Comparisons between groups at baseline will be using two sample *t*-tests for continuous variables and chi-square test for categorical variables.

Differences in treatment effects by randomized group on primary and secondary outcomes at the 12 months follow-up will be assessed. After confirming the assumptions of our data (e.g., using residual plots to examine normality and independence of residuals, and deviations from linearity), we will analyze the continuous outcome measures (A1c, MPR, EQ-5D-5L and DSES-S) using general linear modelling (ANCOVA), adjusting for baseline values. The adjusted mean difference between the two groups will be presented along with its associated 95% CI and *P* value.

Secondary categorical outcomes (proportion of adherents (MPR [3] 80%), self-reported adherence to diabetes medication, MEDAS and IPAQ) will be analyzed using logistic regression, adjusted for baseline values.

Subgroup and adjusted analyses will be carried out to study the effect modification of sex and age, and baseline levels of medication taking.

All analyses will be carried out on an intention-to-treat basis (i.e., all participants are included in the analyses, regardless of whether they receive any exposure to the assigned study treatment).

Missing data will be reported, and the missing data pattern will be explored. If necessary, missing values will be replaced using the multiple imputation model (MICE). Also, we will explore potential bias introduced by attrition by comparing baseline characteristics for the participants lost to follow-up separately [37].

	STUDY PERIOD				
	Invitation	Enrolment	Post-allocation		Close-out
TIMEPOINT	$-t_1$	0	t_1	T_{12}	t_{14}
ENROLMENT:					
Invitation	X				
Eligibility screen		X			
Informed consent		X			
Baseline interview		X			
Allocation		X			
INTERVENTION:					
Diabetext			←	→	
Control group			X	X	
ASSESSMENTS:					
HbA1c		X			X
Medication possession ratio		X		X	
Adherence to meds		X			X
EQ-5D-5L		X			X
DSES-S		X			X
MEDAS		X			X
IPAQ		X			X

Fig. 1. Schedule of enrolment, interventions, and assessments.

Statistical analysis will be performed using Stata v.16 (StataCorp, Texas, USA) and using an alpha of 5% throughout.

3.14. Process evaluation

A process evaluation will be carried out in line with the Medical Research Council guidance on process evaluations for complex interventions [38]. The process evaluation will include: i) a brief ad hoc questionnaire to explore how DiabeText produces change in participants, ii) thirty qualitative individual interviews to explore patient experiences with the intervention and; iii) collection of adverse events and unintended effects of DiabeText.

Participants in the intervention group will be invited to complete an ad hoc questionnaire about their perceptions regarding the extent to which the main behavior change techniques (BCTs) used in DiabeText have generated the intended behavior change in the management of their diabetes. The questionnaire will contain a Likert scale to evaluate the four BCTs most frequently used in DiabeText messages (see Supplementary material 4). The results will be analyzed using descriptive statistics.

For the qualitative evaluation of DiabeText acceptability and perceived utility, we will conduct in-depth individual interviews with thirty participants from the intervention group purposefully sampled to seek heterogeneity in terms of age, gender, duration of diabetes, diabetes complications and comorbidities, baseline self-reported adherence to antidiabetic medication and use of the Internet in their mobiles. Participants will be interviewed following a previously designed and piloted topic guide (Supplementary material 5) which includes three key topics: 1) the evaluation of SMS text message content; 2) the evaluation of SMS text message characteristics and 3) the evaluation of utility and relevance of DiabeText. All interviews will be audio-recorded (with consent), transcribed verbatim, and analyzed thematically.

Adverse effects will be assessed by asking "Do you think that receiving messages to improve diabetes management for 1 year has caused you any harm? If the answer is affirmative, indicate what damage it has caused you."

4. Ethics and dissemination

4.1. Research ethics approval

The study follows the Declaration of Helsinki ethical standards and all the procedures were approved by the Institutional Review Board of the Balearic Islands Health Service Research Ethics (CEI-IB Ref No:

IB4320/20PI).

4.2. Protocol amendments

All protocol modifications before beginning the study will be communicated to the Institutional Review Board of the Balearic Islands Health Service Research Ethics for its approval.

4.3. Consent

Participants' informed consent will be audio-recorded and kept before the start of the study. Participants can voluntarily withdraw their informed consent at any time during the study by contacting the principal investigator by email or by phone.

4.4. Confidentiality

All data collected will be kept anonymous and confidential throughout the study duration. Any data collected prior to the patient's withdrawal will be kept and used by study investigators, as specified in the informed consent. Personal information from potential participants will be only unmasked to the research assistant and the recruitment team of evaluators after signing a confidentiality agreement. The working team will use codification of participants to ensure blinding and personal data protection.

4.5. Access to data

Only the principal investigator and the research manager of the study will have access to the final trial dataset.

4.6. Dissemination policy

Results from the study will be published in a scientific journal and will be also shared with both participants and healthcare professionals involved in the study. If the results are favorable, we will also share the results with local media.

5. Discussion

Spain is one of the top 5 countries in Europe by number of people with diabetes aged between 20 and 79 years old [1]. T2D can be prevented or delayed, and there is accumulating evidence that remission may sometimes be possible [1], but patients with T2D do not always receive the support and information needed to adhere sufficiently to lifestyle and drug treatment [20].

The DiabeText intervention proposed here has the potential to contribute to addressing this important problem. Two systematic reviews by members of our team show that automated SMSs send to mobile devices effectively promote lifestyle changes [16] and medication taking [17]. We propose this type of intervention not only because it is likely to be effective, but also because of its high translational value, as it can be delivered at a low cost (clear potential for cost-effectiveness), and easily implemented widely (high scalability) – constituting therefore a sustainable strategy for Health Services to improve health at the population level. This technology-based solution is highly transferable, as it could also be adapted for its use in other settings and groups of patients. In addition, the intervention would offer, in times of pandemic, a feasible alternative to face-to-face consultations for people with T2D, with a personalized support strategy for improving DSM.

Finally, this intervention would enable personalized remote health care for a broad population, including socially vulnerable populations. This is of special relevance given the affection of T2D in this population group, and the difficulties of access, and therefore representation, of this population group in clinical trials.

5.1. Strengths and limitations

The present RCT will provide strong evidence on mHealth interventions on medication engagement and lifestyle changes in diabetes management. The trial will include a representative sample of people with diabetes, which will allow to generalize the results. Internal validity will be warranted by a randomization process based on allocation sequence generation, blinded to the principal investigator and research staff involved in the study including statisticians. Participants will be aware of their treatment allocation due to the nature of the intervention. A pilot study has already been carried out to assess the appropriateness of intervention messages and logistic procedures [22]. The study meets the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [39] and the guidelines for reporting outcomes in trial protocols: the SPIRIT-Outcomes 2022 extension [40] (see Supplementary material 6). The study will use validated and reliable tools for data collection, objective measures will be collected, such as A1c and MPR and the intervention is based on official guidelines and the latest scientific evidence. However, in terms of limitations, first, rather than ordering laboratory tests to measure A1c, we followed a more pragmatic approach, extracting this data from electronic clinical records when available. In second place, we will use MPR to measure adherence. Medication possession does not necessarily imply medication taking. Pill counting bottles is considered a more reliable method to measure medication taking, but is more expensive (i.e., more limited feasibility in the context of a large trial), and with suboptimal patient acceptability and usability [41]. The advantages of using MPR are that it is usually derived from a reliable and extensive source, it can be implemented in HER and it is relatively inexpensive. In some occasions the delivery of text messages to participants could be lost (e.g., when travelling abroad or the telecommunications company fails to mediate the delivery of the text message) and therefore, some participants would not receive the complete intervention. This study has also the common limitations in e-health trials since participants are not blinded and multiple outcomes are evaluated, increasing the risk for type I error [42]. Lastly, our evaluation of the performance of specific behavior change techniques will be exclusively based on the perceptions of the study participants themselves. While important, this source of data does not offer a complete picture of the mechanisms of the intervention, as it relies on participants being aware of what will change or has changed their behavior.

Why is the research needed?

- T2D is increasingly prevalent, and consequently, the associated comorbidities, loss of quality of life, and loss of autonomy.
- The direct costs of health care treatment for T2D, combined with indirect costs due to labor lack of productivity, are an economic problem for many countries. Interventions to prevent the complications of T2D are needed.
- The development of low-cost and scalable strategies to support diabetes self-management in people with T2D is crucial.

Author contributions

Conceptualization, I.R.-C, J.L.C., IM.S·B, E.A.M., MA.B.M., M.Z.D., L. M.C, E.G.G; methodology, I.R.-C., R.Z.-C., J.L.C., IM.S·B, E.A.M., MA.B. M., M.Z.D., JM.T.A., L.M.C; writing—original draft preparation, R.Z.-C. and I.R.-C.; writing—review and editing, R.Z.-C., I.R.-C., M.A.F.-d., M.J. S.-R, S.M.M., J.K., A.L.R., J.L.C., IM.S·B, E.A.M., MA.B.M., J.R.A. M.Z.D., L.M.C, E.G.G; supervision, I.R.-C, A.L.R., J.L.C., IM.S·B, E.A.M., MA.B. M., M.Z.D., JM.T.A., L.M.C, E.G.G; project administration, I.R.-C. and R. Z.-C.; funding acquisition, I.R.-C. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

I.R.-C., R.Z.-C., M.A.F.-d., M.J.S.-R and E.G.G are owners and developers of the software DiabeText. The resting authors have no conflicts of interest to declare.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107399.

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